HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INCRELEX® safely and effectively. See full prescribing information for INCRELEX®.

INCRELEX® (mecasermin [rDNA origin] injection)

Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Contraindications, Known Hypersensitivity (4.2) 02/2011
Warnings and Precautions, Hypersensitivity and Allergic Reactions, including Anaphylaxis (5.2) 02/2011

----------INDICATIONS AND USAGE----------

INCRELEX® (mecasermin [rDNA origin] injection) is indicated for:

- the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. (1.1)

Limitations of use: INCRELEX® is not a substitute to GH for approved GH indications.

----------DOSAGE AND ADMINISTRATION----------

- INCRELEX® should be administered subcutaneously. (2.2)
- Injection sites should be rotated to avoid lipohypertrophy. (2.2)
- Recommended starting dose: 0.04 to 0.08 mg/kg (40 to 80 micrograms/kg) twice daily. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

- INCRELEX® is a sterile solution supplied in a multiple dose glass vial at a concentration of 10 mg per mL (40 mg per vial). (3)

----------CONTRAINDICATIONS----------

- Active or Suspected Neoplasia (4.1)
- Known Hypersensitivity to mecasermin (4.2)
- Intravenous Administration (4.3)
- Closed Epiphyses (4.4)

----------WARNINGS AND PRECAUTIONS----------

- INCRELEX® should be administered shortly before or after a meal or snack, because it has insulin-like hypoglycemic effects. (5.1)
- Hypersensitivity and Allergic Reactions, including Anaphylaxis: A low number of cases indicative of anaphylaxis requiring hospitalization have been reported. Parents and patients should be informed that such reactions are possible and that if a systemic allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought. (5.2)
- Intracranial Hypertension**:** Funduscopic examination is recommended at the initiation and periodically during the course of INCRELEX® therapy. (5.3)
- Lymphoid Tissue Hypertrophy (tonsillar/adenoidal hypertrophy): Patients should have periodic examinations to rule out potential complications and receive appropriate treatment if necessary. (5.4)
- Slipped Capital Femoral Epiphysis (SCFE): Evaluate any child with onset of a limp or hip/knee pain for possible SCFE. (5.5)
- Progression of Scoliosis: Monitor any child with scoliosis for progression of the spine curve. (5.6)

----------ADVERSE REACTIONS----------

Common INCRELEX®-related adverse reactions in clinical trials include: hypoglycemia (5.1, 6.2), local and systemic hypersensitivity (5.2, 6.2, 6.3), tonsillar hypertrophy (5.4, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-866-837-2422 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, INCRELEX® may cause fetal harm. (8.1)
- Pediatric Use: Safety and effectiveness has not been established in children less than 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [09/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Severe Primary IGF-1 Deficiency (Primary IGFD)

INCRELEX® (mecasermin [rDNA origin] injection) is indicated for the treatment of:

- growth failure in children with severe primary IGF-1 deficiency.
- growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Severe Primary IGF-1 deficiency (IGFD) is defined by:

- height standard deviation score ≤ –3.0 and
- basal IGF-1 standard deviation score ≤ –3.0 and
- normal or elevated growth hormone (GH).

Severe Primary IGFD includes classical and other forms of growth hormone insensitivity. Patients with Primary IGFD may have mutations in the GH receptor (GHR), post-GHR signaling pathway including the IGF-1 gene. They are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

INCRELEX® is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating INCRELEX® treatment.

Limitations of use: INCRELEX® is not a substitute to GH for approved GH indications.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Preprandial glucose monitoring is recommended at treatment initiation and until a well tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue. The dosage of INCRELEX® should be individualized for each patient. The recommended starting dose of INCRELEX® is 0.04 to 0.08 mg/kg (40 to 80 micrograms/kg) twice daily by subcutaneous injection. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses despite adequate food intake, the dose should be reduced. INCRELEX® should be administered shortly before or after (± 20 minutes) a meal or snack. If the patient is unable to eat shortly before or after a dose for any reason, that dose of INCRELEX® should be withheld. Subsequent doses of INCRELEX® should never be increased to make up for one or more omitted dose.

2.2 Administration

INCRELEX® is administered by subcutaneous injection.

INCRELEX® injection sites should be rotated to a different site (upper arm, thigh, buttock or abdomen) with each injection to avoid lipohypertrophy.

INCRELEX® should be administered using sterile disposable syringes and needles. The syringes should be of small enough volume so that the prescribed dose can be withdrawn from the vial with accuracy.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

If using syringes that measure dose in units, doses in mg/kg must be converted to units using the following formula: Weight (kg) x Dose (mg/kg) x 1 mL/10 mg x 100 units/1 mL = units/injection.

3 DOSAGE FORMS AND STRENGTHS

INCRELEX® is a sterile solution available at a concentration of 10 mg per mL (40 mg per vial).

4 CONTRAINDICATIONS

4.1 Active or Suspected Neoplasia

INCRELEX® is contraindicated in the presence of active or suspected malignancy, and therapy should be discontinued if evidence of malignancy develops.

4.2 Known Hypersensitivity

INCRELEX® should not be used by patients who are allergic to mecasermin (rhIGF-1) or any of the inactive ingredients in INCRELEX®, or who have experienced a severe hypersensitivity to INCRELEX® [see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]

4.3 Intravenous Administration

Intravenous administration of INCRELEX® is contraindicated.

4.4 Closed Epiphyses

INCRELEX® should not be used for growth promotion in patients with closed epiphyses.

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

Because INCRELEX® has insulin-like hypoglycemic effects it should be administered shortly before or after (± 20 minutes) a meal or snack. Glucose monitoring and INCRELEX® dose titration are recommended until a well tolerated dose is established (see Dosage 2.1) and subsequently as medically indicated. Special attention should be paid to small children because their oral intake may not be consistent. Patients should avoid engaging in any high-risk activities (e.g., driving, etc.) within 2 to 3 hours after dosing, particularly during the initiation of INCRELEX® treatment until tolerability and a stable dose have been established [see Adverse Reactions (6.1)]. **INCRELEX® should not be administered when the meal or snack is**

omitted. The dose of INCRELEX® should never be increased to make up for one or more omitted doses.

5.2 Hypersensitivity and Allergic Reactions, including Anaphylaxis

Allergic reactions to INCRELEX® have been reported post-marketing. They range from localized (injection site) reactions to systemic reactions, including anaphylaxis requiring hospitalization. Parents and patients should be informed that such reactions are possible and that if a systemic allergic reaction occurs treatment should be interrupted and prompt medical attention should be sought. [see Contraindications (4.2) and Adverse Reactions (6.2, 6.3)]

5.3 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting have occurred in patients treated with INCRELEX®, similar to patients treated with therapeutic doses of growth hormone. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination is recommended at the initiation and periodically during the course of INCRELEX® therapy. [see Adverse Reactions (6.2)]

5.4 Lymphoid Tissue Hypertrophy

Lymphoid tissue (e.g., tonsillar and adenoidal) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of INCRELEX®. Patients should have periodic examinations to rule out such potential complications and receive appropriate treatment if necessary. [see Adverse Reactions (6.2)]

5.5 Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis may occur in patients who experience rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during INCRELEX® therapy should be carefully evaluated.

5.6 Progression of Preexisting Scoliosis

Progression of scoliosis may occur in patients who experience rapid growth. Because INCRELEX® increases growth rate, patients with a history of scoliosis who are treated with INCRELEX® should be monitored for progression of scoliosis.

5.7 Benzyl Alcohol

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

6 ADVERSE REACTIONS

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions:

- Hypoglycemia [see Warnings and Precautions (5.1), Adverse Reaction (6.2)]
- Hypersensitivity and Allergic Reactions, including Anaphylaxis [see Contraindications (4.2), Warnings and Precautions (5.2), Adverse Reaction (6.2)]
- Intracranial hypertension (IH) [see Warnings and Precautions (5.3), Adverse Reaction (6.2]
- Tonsillar and Adenoidal Hypertrophy and related complications [see Warnings and Precautions (5.4) , Adverse Reactions (6.2)]

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies of 71 subjects with Primary IGFD treated for a mean duration of 3.9 years and representing 274 subject-years, no subjects withdrew from any clinical study because of adverse reactions. Adverse reactions to INCRELEX® treatment that occurred in 5% or more of these study participants are listed below by organ class.

Metabolism and Nutrition Disorders: hypoglycemia
General Disorders and Administrative Site Conditions: lipohypertrophy, bruising
Infections and Infestations: otitis media, serous otitis media
Respiratory, Thoracic and Mediastinal Disorders: snoring, tonsillar hypertrophy
Nervous System Disorders: headache, dizziness, convulsions
Gastrointestinal Disorders: vomiting
Ear and Labyrinth Disorders: hypoacusis, fluid in middle ear, ear pain, abnormal tympanometry
Cardiac Disorders: cardiac murmur
Musculoskeletal and Connective Tissue Disorders: arthralgia, pain in extremity
Blood and Lymphatic System Disorders: thymus hypertrophy
Surgical and Medical Procedures: ear tube insertion

Hypoglycemia was reported by 30 subjects (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five subjects had severe hypoglycemia (requiring assistance and treatment) on one or more occasion and 4 subjects experienced hypoglycemic seizures/loss of consciousness on one or more occasion. Of the 30 subjects reporting hypoglycemia, 14 (47%) had a history of hypoglycemia prior to treatment. The frequency of hypoglycemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycemia was generally avoided when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of INCRELEX®.

Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the procedure in all three cases.

Intracranial hypertension occurred in three subjects. In two subjects the events resolved without interruption of INCRELEX® treatment. INCRELEX® treatment was discontinued in the third subject and resumed later at a lower dose without recurrence.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment. Rise in levels of these serum enzymes did not lead to treatment discontinuation. ALT elevations were occasionally noted during treatment.

Renal and splenic lengths (measured by ultrasound) increased rapidly on INCRELEX® treatment during the first years of therapy. This lengthening slowed down subsequently; though in some patients, renal and/or splenic length reached or surpassed the 95th percentile. Renal function (as defined by serum creatinine and calculated creatinine clearance) was normal in all patients, irrespective of renal growth.

Elevations in cholesterol and triglycerides to above the upper limit of normal were observed before and during treatment.

Echocardiographic evidence of cardiomegaly/valvulopathy was observed in a few individuals without associated clinical symptoms. The relation of these cardiac changes to drug treatment cannot be assessed due to underlying disease and the lack of a control group.

Thickening of the soft tissues of the face was observed in several patients and should be monitored during INCRELEX® treatment.

As with all therapeutic proteins, there is potential for immunogenicity. Anti-IGF-1 antibodies were present at one or more of the periodic assessments in 14 of 23 children with Primary IGFD treated for 2 years. However, no clinical consequences of these antibodies were observed (e.g., attenuation of growth). The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody

(including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to INCRELEX® with the incidence of antibodies to other products may be misleading.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of INCRELEX®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Systemic hypersensitivity; *anaphylaxis, generalized urticaria, angioedema, dyspnea*

In the post-marketing setting, the frequency of cases indicative of anaphylaxis was estimated to be 0.3%. Symptoms included hives, angioedema, and dyspnea, and some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients.

Local allergic reactions at the injection site; *pruritis, urticaria.*

Skin and Subcutaneous Tissue Disorders: alopecia, hair texture abnormal.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Studies to assess embryo-fetal toxicity evaluated the effects of INCRELEX® during organogenesis in Sprague Dawley rats given 1, 4, and 16 mg/kg/day and in New Zealand White rabbits given 0.125, 0.5, and 2 mg/kg/day, administered intravenously. There were no observed embryo-fetal developmental abnormalities in rats given up to 16 mg/kg/day (20 times the maximum recommended human dose [MRHD] based on body surface area [BSA] comparison). In the rabbit study, the NOAEL for fetal toxicity was 0.5 mg/kg (2 times the MRHD based on BSA) due to an increase in fetal

death at 2 mg/kg. INCRELEX® displayed no teratogenicity or maternal toxicity in rabbits given up to 2 mg/kg (8 times the MRHD based on BSA).

The effects of INCRELEX® on an unborn child have not been studied. Therefore, there is insufficient medical information to determine whether there are significant risks to a fetus.

8.3 Nursing Mothers

Excretion of INCRELEX® in human milk has not been studied. As many drugs are excreted in human milk, caution should be exercised when INCRELEX® is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years of age have not been established.

8.5 Geriatric Use

The safety and effectiveness of INCRELEX® in patients aged 65 and over has not been established.

8.6 Renal Impairment

No Studies have been conducted in Primary IGFD children or adult subjects with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No studies have been conducted in Primary IGFD children or adult subjects with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Treatment of acute overdose should be directed at reversing hypoglycemia. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous glucose or parenteral glucagon may be required to reverse the hypoglycemic effects.

A small number of overdose cases have been reported in the post-marketing experience. In one case of acute overdose, a 3-year old patient experienced hypoglycemia after receiving one 4 mg dose of INCRELEX® (a 10-fold increase beyond the prescribed dose). The event resolved following treatment with IV glucose.

Long term overdosage with INCRELEX® may result in signs and symptoms of acromegaly.

11 DESCRIPTION

INCRELEX® (mecasermin [rDNA origin] injection) contains human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges and a molecular weight of 7649 daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The rhIGF-1 protein is synthesized in bacteria (*E. coli*) that have been modified by the addition of the gene for human IGF-1.

INCRELEX® is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial of INCRELEX® contains 10 mg per mL mecasermin, 9 mg per mL benzyl alcohol, 5.84 mg per mL sodium chloride, 2 mg per mL polysorbate 20, and 0.05M acetate at a pH of approximately 5.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Insulin-like growth factor-1 (IGF-1) is a key hormonal mediator on statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver, and other tissues, and stimulates the synthesis/secretion of IGF-1. In target tissues, the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes resulting in statural growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

12.2 Pharmacodynamics

The following actions have been demonstrated for endogenous human IGF-1:

Tissue Growth – 1) Skeletal growth occurs at the cartilage growth plates of the epiphyses of bones where stem cells divide to produce new cartilage cells or chondrocytes. The growth of chondrocytes is under the control of IGF-1 and GH. The chondrocytes become calcified so that new bone is formed allowing the length of the bones to increase. This results in skeletal growth until the cartilage growth plates fuse at the end of puberty. 2) Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activities that lead to an increased number of cells in the body. 3) Organ growth: Treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Carbohydrate Metabolism –IGF-1 suppresses hepatic glucose production and stimulates peripheral glucose utilization and therefore has a hypoglycemic potential. IGF-1 has inhibitory effects on insulin secretion.

12.3 Pharmacokinetics

Absorption – The absolute bioavailability of rhIGF-1 after subcutaneous administration in healthy subjects is estimated to be close to 100%. However, the absolute bioavailability of INCRELEX® given subcutaneously to subjects with primary insulin-like growth factor-1 deficiency (Primary IGFD) has not been determined.

Distribution – In blood, IGF-1 is bound to six IGF binding proteins, with > 80% bound as a complex with IGFBP-3 and an acid-labile subunit. IGFBP-3 is greatly reduced in subjects with severe Primary IGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects. The total IGF-1 volume of distribution after subcutaneous administration in subjects with severe Primary IGFD is estimated to be 0.257 (± 0.073) L/kg at an INCRELEX® dose of 0.045 mg/kg, and is estimated to increase as the dose of INCRELEX® increases.

Elimination – IGF-1 is metabolized by both liver and kidney. The mean terminal $t_{1/2}$ after single subcutaneous administration of 0.12 mg/kg INCRELEX® in pediatric subjects with severe Primary IGFD is estimated to be 5.8 hours. Clearance of INCRELEX® is inversely proportional to IGF binding protein-3 (IGFBP-3) levels. CL/F is estimated to be 0.04 L/hr/kg at 0.5

micrograms/mL of IGFBP-3, and 0.01 L/hr/kg at 3 micrograms/mL IGFBP-3; the latter is the median IGFBP-3 in subjects with normal IGF-1 serum levels.

Gender – In children with Primary IGFD there were no apparent differences between males and females in the pharmacokinetics of INCRELEX®.

Race –The effect of race on pharmacokinetics of INCRELEX® has not been studied.

Summary of INCRELEX® Single-Dose Pharmacokinetic Parameters in Children with Severe Primary IGFD (0.12 mg/kg, SC)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8} (hr*ng/mL)	$t_{1/2}$ (hr)	Vd/F (L/kg)	CL/F (L/hr/kg)
n	3	3	3	3	12[a]	12[a]
Mean	234	2	2932	5.8	0.257	0.0424
CV%	23	0	50	64	28	38

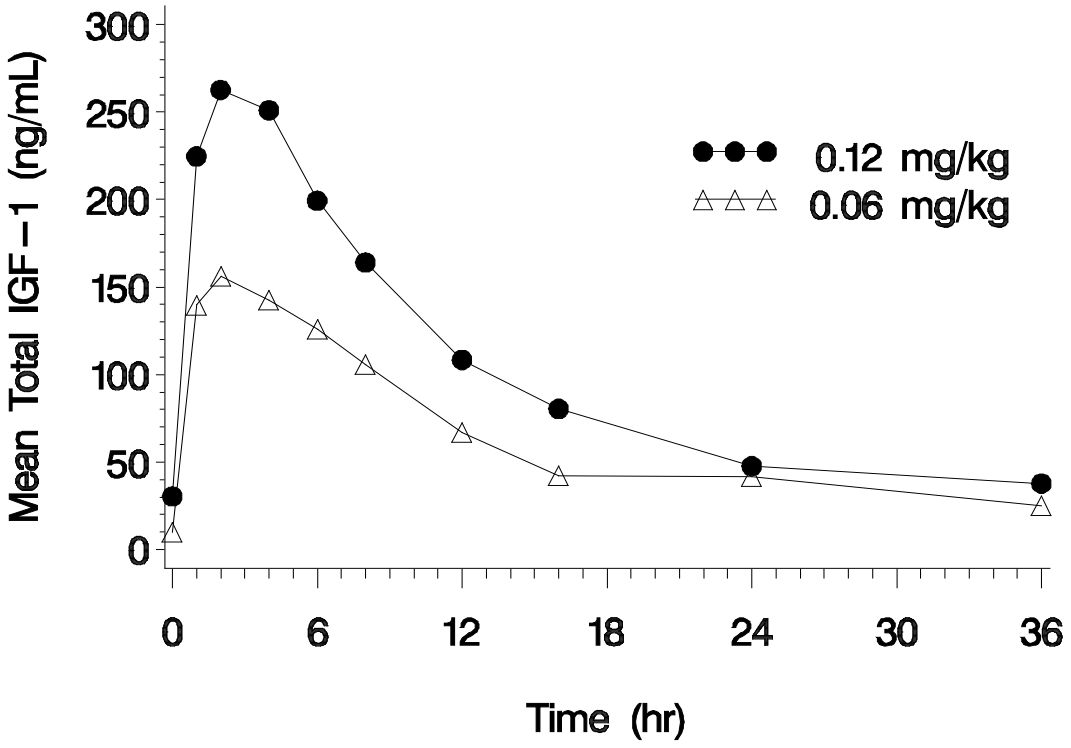
C_{max} = maximum concentration; T_{max} = time of maximum concentration; AUC_{0-8} = area under the curve; $t_{1/2}$ = half-life; Vd/F = apparent volume of distribution; CL/F = apparent systemic clearance; SC = subcutaneous injection; CV% = coefficient of variation in %.

Male/female data combined, ages 12 to 22 years.

[a] Data represents 3 subjects each at doses 0.015, 0.03, 0.06, and 0.12 mg/kg SC.

PK parameters based on baseline adjusted plasma concentrations.

Mean Total IGF-1 Concentration after a Single Subcutaneous Dose of INCRELEX® in Children with Severe Primary IGFD (0.06 mg/kg and 0.12 mg/kg, n = 3 per group)



Renal impairment– No studies have been conducted in Primary IGFD children with renal impairment.

Hepatic impairment– No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of rhIGF-1 in Primary IGFD children with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: INCRELEX® was tumorigenic in rats in a study using doses of 0, 0.25, 1, 4, and 10 mg/kg/day by subcutaneous injection for up to 2 years. The incidence of adrenal medullary hyperplasia and pheochromocytoma increased in male rats given ≥1

mg/kg/day (≥ 1 times the clinical exposure with the maximum recommended human dose [MRHD] based on AUC) and in female rats at all dose levels (≥ 30% of the clinical exposure with the MRHD based on AUC). The incidence of keratoacanthoma in the skin increased in male rats given 4 and 10 mg/kg/day (≥ 4 times the MRHD). The incidence of mammary gland carcinoma in male rats increased in animals treated with 10 mg/kg/day (7 times the MRHD based on AUC). Only doses that exceeded the maximum tolerated dose (MTD) (based on excess mortality secondary to IGF-1 induced hypoglycemia) caused skin and mammary tumors.

Mutagenesis: INCRELEX® was not clastogenic in the in vitro chromosome aberration assay and the in vivo mouse micronucleus assay.

Impairment of fertility: INCRELEX® had no effects on fertility in rats using intravenous doses 0.25, 1, and 4 mg/day (up to 4 times the clinical exposure with the MRHD based on AUC.)

14 CLINICAL STUDIES

14.1 Effects of INCRELEX® Treatment in Children with Severe Primary Insulin-like Growth Factor-1 Deficiency (Primary IGFD)

Five clinical studies (four open-label and one double-blind, placebo-controlled), with subcutaneous doses of INCRELEX® generally ranging from 0.06 to 0.12 mg/kg (60 to 120 micrograms/kg) administered twice daily, were conducted in 71 pediatric subjects with severe Primary IGFD. Patients were enrolled in the trials on the basis of extreme short stature, slow growth rates, low IGF-1 serum concentrations, and normal growth hormone secretion. Data from these 5 clinical studies were pooled for a global efficacy and safety analysis. Baseline characteristics for the patients evaluated in the primary and secondary efficacy analyses were (mean, SD): chronological age (years): 6.7 ± 3.8; height (cm): 84.8 ± 15.3 cm; height standard deviation score (SDS): -6.7 ± 1.8; height velocity (cm/yr): 2.8 ± 1.8; height velocity SDS: -3.3 ± 1.7; IGF-1 (ng/mL): 21.6 ± 20.6; IGF-1 SDS: -4.3 ± 1.6; and bone age (years): 4.2 ± 2.8. Sixty-one subjects had at least one year of treatment. Fifty-three (87%) had Laron Syndrome; 7 (11%) had GH gene deletion, and 1 (2%) had neutralizing antibodies to GH. Thirty-seven (61%) of the

subjects were male; forty-eight (79%) were Caucasian. Fifty-six (92%) of the subjects were pre-pubertal at baseline.

Annual results for height velocity, height velocity SDS, and height SDS are shown in Table 1. Pre-treatment height velocity data were available for 58 subjects. The height velocities at a given year of treatment were compared by paired t-tests to the pre-treatment height velocities of the same subjects completing that treatment year.

Table 1: Annual Height Results by Number of Years Treated with INCRELEX®

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
N	58	58	48	38	23	21	20	16	13
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.5)	5.5 (1.8)	4.7 (1.6)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.3 (1.1)
Mean (SD) for change from pre-treatment		+5.2 (2.6)	+2.9 (2.4)	+2.3 (2.4)	+1.5 (2.2)	+1.5 (1.8)	+1.5 (1.7)	+1.0 (2.1)	+0.7 (2.5)
P-value for change from pre-treatment [1]		<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
Height Velocity SDS									
N	58	58	47	37	22	19	18	15	11
Mean (SD)	-3.3 (1.7)	1.9 (3.0)	-0.2 (1.6)	-0.2 (2.0)	-0.7 (2.1)	-0.6 (2.1)	-0.4 (1.4)	-0.4 (1.9)	-0.4 (1.9)
Mean (SD) for change from pre-treatment		+5.2 (3.1)	+3.1 (2.3)	+2.9 (2.3)	+2.2 (2.2)	+2.5 (2.2)	+2.7 (1.7)	+2.5 (2.1)	+2.7 (2.8)
Height SDS									
N	61	61	51	40	24	21	20	16	13
Mean (SD)	-6.7 (1.8)	-5.9 (1.8)	-5.6 (1.8)	-5.4 (1.8)	-5.5 (1.9)	-5.6 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (2.0)
Mean (SD) for change from pre-treatment		+0.8 (0.5)	+1.2 (0.8)	+1.4 (1.1)	+1.3 (1.2)	+1.4 (1.3)	+1.4 (1.2)	+1.4 (1.1)	+1.5 (1.1)

Pre-Tx = Pre-treatment; SD = Standard Deviation; SDS = Standard Deviation Score

[1] P-values for comparison versus pre-treatment values are computed using paired t-tests.

Forty-nine subjects were included in an analysis of the effects of INCRELEX® on bone age advancement. The mean ± SD change in chronological age was 4.9 ± 3.4 years and the mean ± SD change in bone age was 5.3 ± 3.4 years.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC-15054-1040-5 INCRELEX® is supplied as a 10 mg per mL sterile solution in multiple dose glass vials (40 mg per vial).

Before Opening – Vials of INCRELEX® are stable when refrigerated [2º to 8ºC (35º to 46ºF)]. Avoid freezing the vials of INCRELEX®. Protect from direct light. Expiration dates are stated on the labels.

After Opening – Vials of INCRELEX® are stable for 30 days after initial vial entry when stored at 2º to 8ºC (35º to 46ºF). Avoid freezing the vials of INCRELEX®. Protect from direct light.

Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. INCRELEX® should not be used after its expiration date. Keep refrigerated and use within 30 days of initial vial entry. Remaining unused material should be discarded.

17 PATIENT COUNSELING INFORMATION

Patients and/or their parents should be instructed in the safe administration of INCRELEX®. INCRELEX® should be given shortly before or after (20 minutes on either side of) a meal or snack. **INCRELEX® should not be administered when the meal or snack is omitted.** The dose of INCRELEX® should never be increased to make up for one or more omitted doses. INCRELEX® therapy should be initiated at a low dose and the dose should be increased only if no hypoglycemia episodes have occurred after at least 7 days of dosing. If severe hypoglycemia or persistent hypoglycemia occurs on treatment despite adequate food intake, INCRELEX® dose reduction should be considered. Providers should educate patients and caregivers on how to recognize the signs and symptoms of hypoglycemia.

INCRELEX® treatment may need to be discontinued if allergic reactions occur. Providers should educate patients and caregivers on the identification of signs and symptoms of serious allergic reactions to INCRELEX® and the need to seek prompt medical contact should such a reaction occur.

Patients and/or parents should be thoroughly instructed in the importance of proper needle disposal. A puncture-resistant container should be used for the disposal of used needles and/or syringes (consistent with applicable state requirements). Needles and syringes must not be reused.

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